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EXAMINER

LIU, SUE XU

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Claim Status

1. Claims 2-26, 39, 40, 46 and 47 have been cancelled as filed on 3/12/09.
Claims 54 and 55 have been added as filed on 3/12/09.
Claims 1, 27-38, 41-45 and 48-55 are currently pending.
Claims 1, 27-37, 52 and 53 have been withdrawn.
Claims 38, 41-45, 48-51, 54 and 55 are being examined in this application.

Election/Restrictions

2. Applicant's election without traverse of Group 3 (claims 38-51) in the reply filed on 5/19/2008 is as previously acknowledged. The newly added claims 54 and 55 are grouped with the Group 3 invention.
3. As previously acknowledged, Claims 1, 27-37, 52 and 53 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/19/08.

Priority

4. This application is filed under 35 U.S.C 371 of PCT/GB03/00291 (filed on 1/23/2003).

Specification

5. Applicant's filing of amendments to the specification and drawings to remove hyperlink, correcting typographic errors and comply with the Sequence Rule (as filed on 3/12/09 and 4/10/09) are acknowledged and entered.

Claim Objection(s) / Rejection(s) Withdrawn

6. In light of applicants' amendments to the claims, the following claim rejection(s) as set forth in the previous office action is(are) withdrawn:

A.) Claims 38-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B.) Claims 38-41, 45-47 and 51 are rejected under **35 U.S.C. 102(b)** as being anticipated by Shibata et al (EP 0989136; 3/29/2000; cited in IDS).

C.) Claims **38-42**, **45-47** and **51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibata et al (EP 0989136; 3/29/2000; cited in IDS), in view of Thornborrow et al (JBC. Vol.274(47): 33747-33756; 1999; cited in IDS).

D.) Claims **38-47** and **51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibata et al (EP 0989136; 3/29/2000; cited in IDS) and Thornborrow et al (JBC. Vol.274(47): 33747-33756; 1999; cited in IDS), as applied to claims 38-42, 45-47 and 51 above, and further in view of Skarnes (US 5,767,336; 6/16/1998).

E.) Claims **38-51** are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibata et al (EP 0989136; 3/29/2000; cited in IDS), Thornborrow et al (JBC. Vol.274(47): 33747-33756; 1999; cited in IDS), and Skarnes (US 5,767,336; 6/16/1998) as applied to claims 38-47 and 51 above, and further in view of Noaln et al (WO 97/27212; 7/31/1997; cited in IDS).

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Claim Objection(s) / Rejection(s) Maintained***Double Patenting***

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 38, 41-45, 48-51, 54 and 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 28-49 of copending Application No. 10/493,582 (PGPUB 20070128657; hereinafter referred to as the ‘582 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the ‘582 application read on the instant claimed method. The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

The ‘582 application claims a method of screening a library of peptides using reporter system as recited in claim 1, which reads on the method of the instant claim 38.

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The '582 application also claims various components of the reporter system, the target protein, the size of the library, etc., (as recited in claims 28-39), which reads on the instant claimed reporter system, target protein, etc., as recited in the instant claims 39-51.

The '582 application also claims the screening assay is using p53 as the target binding proteins (e.g. claim 31), which reads on the p53 of the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion and Answer to Argument

9. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants state "applicant will consider filing a terminal disclaimer..." (Reply, p.20).

Applicants have neither filed a terminal disclaimer nor provided traversal over the above rejection. Thus, the above rejection is maintained for the reasons of record.

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New Claim Objection(s) / Rejection(s)

Claim Objections

10. Claim 38 is objected to because of the following informalities: The term “a” in line 1 of step (a) of claim 38 should be replaced with “the”. That is claim should recite “(a) introducing the library of peptides...” Appropriate correction is required.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Shibata, Noaln, Daniels

12. Claims **38, 41, 42, 45, 48-51, 54** and **55** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Shibata** et al (EP 0989136; 3/29/2000; cited in IDS), **Noaln** et al (WO 97/27212; 7/31/1997; cited in IDS), **Daniels** et al., (J. Mol. Biol. Vol. 243: 639-652; 1994), and if necessary, in view of **Tenson** et al. (J Biol. Chem. Vol.272(28): 17425-17430; 1997; cited in IDS). This rejection is necessitated by applicant's amendments to the claims.

The instant claims recite “a method of screening a library of peptides of 2 to 8 amino acids in length for the ability of members of the library to restore or modify the function of p53 in an intra-cellular environment, the method comprising:

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(a) introducing a library of peptides of 2 to 8 amino acids in length into host cells having a reporter system that allows for the identification of those cells in which the function of p53 has been restored or modified; and

(b) identifying those cells in which the function of p53 has been restored or modified” and/or variations thereof.

Shibata et al, throughout the publication, teach various methods of screening a library of peptides with a reporter gene assay system (e.g. Abstract; pp.19+).

For **claims 38, 54 and 55**: “(a) *introducing a library of peptides... into host cells having a reporter system...*” The reference teaches cells comprising a reporter system (e.g. pp.19-20, bridging), which read on the host cells having a reporter system of the instant claims. The reference also teaches introducing “test compounds” (i.e. a library of peptides; p.3, lines 30+) into the host cells (e.g. p.20, lines 40+; Tables 3-4), which reads on the step of introducing the library into host cells as recited in the instant claims. The reference also teaches measuring the activation of p53 (i.e. restoration/modification of p53 activity) through the reporter gene expression (e.g. pp.19+; [0095]), which reads on “restored or modified” p53 function of the instant claims.

“(b) *identifying those cells in which the function of p53...*” The reference teaches measuring the activity of the reporter cells and identifying the compounds that activated the reporter activity (e.g. p.21, Table 4), which cells containing the test peptides are “identified” through the measure of their reporter gene activities. The reference also identified the sequences of the peptides that activated/modified p53 function (e.g. p.22, [0110]).

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“(c) identifying the peptide in the cell...”: The reference teaches the identity of the testing peptides as the amino acid sequences of the peptides are identified (e.g. pp.20+; pp.31+; Abstract).

For **claim 41**: The reference teaches the reporter system comprise a reporter gene (e.g. luciferase) and a “P53 responsive element” in the transcription regulatory region (e.g. pp.19-20), which the reporter gene construct reads on the reporter system.

For **claim 45**: The reference teaches transfecting the reporter plasmid into the host cells (e.g. [0104]+), which reads on the transfection step.

For **claim 51**: The reference teaches using human cells (e.g. p.20, lines 46+), which reads on the eukaryotic cells.

Shibata et al do not explicitly teach the peptides of the library have lengths ranging from 2 to 8 amino acids long as recited in **clms 38, 54 and 55**. The Shibata reference also does not explicitly teach the size of the peptide library recited in **clm 50**. The reference also does not explicitly teach the peptide library has the sequence of M-G/M/V-(X)_n as recited in **clm 49**. The Shibata reference also does not explicitly teach the “introducing a library comprising nucleic acid constructs...” as recited in **clms 48 and 54**.

However, **Noaln** et al., throughout the publication, teach making and using peptide libraries in target screening assays (e.g. Abstract).

For **claims 38, 54 and 55**: The reference teaches the method steps of (a) introducing a molecular library into cells, (b) screening the cells, (c) isolate/identify cell with altered

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phenotype, (d) isolate/identify the library members (e.g. p.3, lines 6+), which reads on the screening method steps of the instant claims. The reference also teaches peptides with various lengths such as 9 amino acid residues (e.g. p.22, lines 15+).

The reference also teaches the screening assay can be used to identify library members (peptides) that can “reactivate” or “compensate” for p53 activity, especially in tumor cells (e.g. p.37, lines 25+).

For **claims 48 and 54**: The reference teaches generating nucleic acid constructs encoding for the peptides and introducing the constructs into cells (e.g. p.23), which reads on DNA constructs as well as the method step of introducing DNA into cells.

For **claim 50**: The reference also teaches the size of the peptide library are various such as 10^7 peptides (e.g. p.20, lines 4+), which reads on the library size.

For **claim 49**: The reference also teaches using peptide library with conserved consensus amino acid residues such as the ones with M and G residues (e.g. p.7; p.8; p.22), which reads on the conserved sequence.

In addition, **Daniel** et al., throughout the publication, teach making and using peptides for binding to p53 protein (e.g. Abstract). The reference teaches “hexameric” (i.e. 6 amino acids in length) peptide library is used to screening for peptides that bind to p53 (e.g. Abstract; pp.640+). The reference also teaches the need to study p53 protein as well as its interacting peptides (e.g. p. 639).

Further, if necessary, **Tenson** et al., throughout the publication, teach minigene expression libraries (i.e. peptide libraries) comprising transforming host cells with a library of

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nucleic acid constructs encoding peptides of various lengths and formula MX_n , MVX_n , MMX_n , or MGX_n and culturing the host cells to allow for expression of the peptide library (e.g. Abstract; Figures 2B, 3, 4; pp.17425+). The reference teaches peptides having lengths such as 3-6 amino acids (e.g. Abstract; Figures 2 and 3).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to screen a library of peptides having various lengths (such as less than 8 amino acids), a library with various sizes and a peptide library with various sequences as well as using a library of encoding nucleic acid constructs.

A person of ordinary skill in the art would have been motivated at the time of the invention to use a library of peptides of small lengths such as 3 to 6 amino acids, because Daniel teaches the need to identify small peptides that can interact with p53 (such as the ones with 6 amino acids). In addition, because both the cited references (such as Shibata, Daniel and Tenson) teach methods of using/screening peptide libraries having various lengths, it would have been obvious to one skilled in the art to substitute one type of peptides (e.g. peptides with longer lengths such as 15 amino acids) for the other (e.g. peptides with shorter lengths such as 3-6 amino acids) to achieve the predictable result of screening/using peptide libraries to identify peptides of interest based on the purpose of the experimental design.

A person of ordinary skill in the art would have been motivated at the time of the invention to use peptide library of various sizes, because peptide library of various sizes are known and routine in the art as taught by Noaln et al. In addition, it would have been obvious to one of ordinary skill in the art to apply the standard technique of generating peptide library of

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large size (such as at least 500 different members) as taught by Noaln et al, to improve the peptide library diversity and screening efficiency for the predictable result of enabling standard peptide library screening assays.

A person of ordinary skill in the art would have been motivated at the time of the invention to screen peptide library generated with certain conserved consensus amino acid residues depending on the screening target, because using peptides with conserved amino acid residues for targeted screening are known and routine in the art as taught by Noaln et al. In addition, because both of the Shibata and the Noaln references teaches screening peptide libraries, it would have been obvious to one skilled in the art to substitute one type of peptide libraries (with one type of consensus sequence) for the other (e.g. sequences with M and G residues) to achieve the predictable result of screening peptide libraries in a reporter gene assay system.

A person of ordinary skill in the art would have been motivated at the time of the invention to use encoding nucleic acid constructs to introduce peptides into cells, because using nucleic acid constructs offer the advantages of providing in vivo expressed peptides inside the cells, and using nucleic acid constructs are known and routine in the art as taught by Noaln et al. and Tenson et al. In addition, it would have been obvious to one of ordinary skill in the art to apply the standard technique of using encoding nucleic acid constructs to produce peptides in cells as taught by Noaln et al. and Tenson et al., to improve the peptide library availability inside host cells for the predictable result of enabling standard peptide library screening assays inside cells.

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A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of using reporter gene assays with various elements.

Shibata, Noaln, Daniels, Thornborrow

13. Claims **38, 41, 42, 45, 48-51, 54** and **55** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Shibata** et al (EP 0989136; 3/29/2000; cited in IDS), **Noaln** et al (WO 97/27212; 7/31/1997; cited in IDS), **Daniels** et al., (J. Mol. Biol. Vol. 243: 639-652; 1994), and **Tenson** et al. (J Biol. Chem. Vol.272(28): 17425-17430; 1997; cited in IDS), as applied to claims 38, 41, 45, 48-51, 54 and 55 above, and further in view of **Thornborrow** et al (JBC. Vol.274(47): 33747-33756; 1999; cited in IDS).

Shibata et al, throughout the publication, teach various methods of screening a library of peptides with a reporter gene assay system as discussed supra.

Noaln et al., throughout the publication, teach making and using peptide libraries in target screening assays, as discussed supra.

Daniel et al., throughout the publication, teach making and using peptides for binding to p53 protein, as discussed supra.

Tenson et al., throughout the publication, teach minigene expression libraries for introducing peptide libraries into cells, as discussed supra.

The above rejection over Shibata, Noaln, Daniel and Tenson references under 35 USC 103(a) is herein incorporated by reference in its entirety.

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The combination of the Shibata and Thornborrow references does not explicitly teach the reporter gene construct is linked to a p21 or BAX promoter as recited in **claim 42**.

However, **Thornborrow** et al. teach using reporter gene constructs with either p21 or BAX promoter region that contains p53 response elements (or p53 binding regions) (e.g. p.33748, left col., para 3), which the promoters read on the promoters recited in **claim 42**. The reference also teaches the p21 and BAX promoters are regulated by p53, and the regulation is important in various cellular mechanisms (e.g. p.33747). Thus, there is a great need to understand the interaction between the promoters and p53.

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to use p21 or BAX promoter region in the reporter gene construct for testing p53.

A person of ordinary skill in the art would have been motivated at the time of the invention to use p21 or BAX promoter region in the reporter gene construct for assaying p53, because p21 and BAX are known to substrate for p53 as taught by both Shibata et al and Thornborrow et al. In addition, due to the need to understand the interaction between p53 and its regulatory elements for various important cellular functions, a person of ordinary skill in the art would have been motivated at the time of the invention to use p21 or BAX promoters. In addition, because the both references teach using reporter gene construct with p53 responsive elements (such as various promoter regions) for testing p53, it would have been obvious to one skilled in the art to substitute one known p53 responsive element (SV40 early promoter region)

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for the other (p21 or BAX promoter region) to achieve the predictable result of detecting measuring/testing p53 activation/function in a reporter gene assay system.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since both of the cited references have demonstrated the success of using reporter gene assays with various elements.

Shibata and Others

14. Claims **38**, **41-45**, **48-51**, **54** and **55** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Shibata** et al (EP 0989136; 3/29/2000; cited in IDS), **Noaln** et al (WO 97/27212; 7/31/1997; cited in IDS), **Daniels** et al., (J. Mol. Biol. Vol. 243: 639-652; 1994), **Tenson** et al. (J Biol. Chem. Vol.272(28): 17425-17430; 1997; cited in IDS), and **Thornborrow** et al (JBC. Vol.274(47): 33747-33756; 1999; cited in IDS), as applied to claims 38, 41, 42, 45, 48-51, 54 and 55 above, and further in view of **Skarnes** (US 5,767,336; 6/16/1998; cited previously).

The combination of the Shibata, Noaln, Daniel, Tenson and Thornborrow references teaches methods of screening for peptides that can modify or restore p53 activity in cell reporter assay system, as discussed supra.

The above rejection over Shibata, Noaln, Daniel, Tenson and Thornborrow references under 35 USC 103(a) is herein incorporated by reference in its entirety.

The combination of Shibata, Noaln, Daniel, Tenson and Thornborrow references does not explicitly teach the reporter gene product include a secretion signal peptide as recited in **clm 43**, and a transmembrane domain as recited in **clm 44**.

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However, **Skarnes** et al. teach generating reporter gene construct having secretion signals and transmembrane domains (e.g. cols.3, lines 20+), which read on the signal peptide and transmembrane domain as recited in **clms 43** and **44**. The reference also teaches the need to generate reporter gene encoding for fusion proteins having secretion signal and transmembrane domains for studying secretory proteins (e.g. cols.1-2).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate reporter proteins with secretion signal and transmembrane domains.

A person of ordinary skill in the art would have been motivated at the time of the invention to generate fusion reporter proteins having secretion signals and transmembrane domain, because including secretion signals and transmembrane in fusion reporter proteins are known and routine in the art as taught by Skarnes. As the Skarnes reference teaches the advantages of including secretion signals and transmembrane domains so that secretory proteins can be conveniently studied (e.g. cols.1-2), a person ordinary skill in the art would have been motivated at the time of the invention to generate fusion reporter proteins having secretion signals and transmembrane domain. In addition, it would have been obvious to one of ordinary skill in the art to apply the standard technique of generating fusion reporter proteins having secretion signals and transmembrane domains, as taught by Skarnes, to improve the reporter protein assay for the predicable result of enabling standard reporter gene assay system.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of using reporter gene assays with various elements.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Sue Liu/
Primary Examiner, AU 1639
3/19/2010